

Drug Class Review on Newer Antiemetics



Update #1: Preliminary Scan Report

November 2006

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Original Final Report January 2006 (searches through February 2005)

SCOPE AND KEY QUESTIONS:

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Question 1: What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting?

Key Question 2: What is the comparative tolerability and safety of Newer Antiemetics when used to treat or prevent nausea and/or vomiting?

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities for which one Newer Antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s):

Adults or Children at risk for or with nausea and/or vomiting (including retching) related to the following therapies and conditions:

- Chemotherapy*
- Radiation Therapy
- Post-Operative
- Pregnancy

* In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999^{13, 14} to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetogenic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs – i.e., it classifies the chemotherapeutic agents according to the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as “1” on this scale have a low emetogenic potential, while agents rated as “5” are considered to be severely emetogenic (a >90% chance of emesis in patients).

Interventions

Table 1. Antiemetic Drug Indications and Recommended Doses

Generic Name	Trade Name	FDA Approved Indications and Dosage in Adults	FDA Approved Indications and Dosage in Children
Aprepitant	Emend®	Chemotherapy: Day 1: 125 mg po once Days 2 & 3: 80 mg po once <i>Emend is to be given for 3 days in conjunction with a regimen containing a 5HT3-antagonist and a corticosteroid</i>	Chemotherapy: Dose determined by doctor
Dolasetron	Anzemet®	Chemotherapy: 100 mg po once (up to 1 hr before chemo) 1.8 mg/kg iv once (up to 30 min before chemo); Alternatively, a fixed dose of 100mg iv can be administered over 30sec. PONV, prevention: 100 mg po once (up to 2 hrs before surgery) 12.5 mg iv once (15 min. before anesthesia ends) PONV, established: 12.5 mg iv once (at onset of symptoms)	Chemotherapy (for children 2-16years): 1.8 mg/kg po & iv once, max. 100mg (up to 30 min before chemo) PONV, prevention: 0.35 mg/kg iv once, max. 12.5 mg (15 min before anesthesia ends) 1.2 mg/kg po once, max. 100mg (up to 2 hrs before surgery) PONV, established: 0.35 mg/kg iv once, max. 12.5mg (at onset of symptoms)
Granisetron	Kytril®	Chemotherapy: 2 mg po once (up to 1 hr before chemo) 0.10mg/kg iv once (up to 30 min before chemo) PONV, prevention: 1 mg iv once (before induction or before reversal of anesthesia) PONV, established: 1 mg iv once Radiation: 2 mg po once	Chemotherapy: 0.10 mg/kg iv once (up to 30 min before chemo)

Ondansetron	Zofran®	Chemotherapy: <i>Moderately emetogenic:</i> 8 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given twice daily <i>Highly emetogenic:</i> single 24 mg tablet 30 min before chemo; 32 mg iv once (30 min before chemo) or 0.15 mg/kg tid (1 st dose is infused 30 min before chemo starts) PONV, prevention: 4 mg iv once (immediately before induction of anesthesia) 16 mg po (tablet or orally disintegrating tablet) once (1 hr before anesthesia induction) (20 mL if oral solution given) PONV, established: 4 mg iv or im once (at onset of symptoms) Radiation: 8 mg po (tablet or orally disintegrating tablet) X3 (10 mL X3 if oral solution given) (1 st dose 1-2 hours before radiation)	Chemotherapy <i>Moderately emetogenic:</i> for patients aged 12 years and above, the dosage is the same as in adults; for patients 4-11 years the dose is 4 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given three times daily 0.15mg/kg iv once (30 min before chemo) PONV, prevention (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg PONV, established (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg
Palonosetron	Aloxi®	Chemotherapy: 0.25 mg iv once (up to 30 minutes before chemo)	Chemotherapy: Dose determined by doctor

po = (*per os*) orally

iv = intravenous

im = intramuscular

Effectiveness outcomes

Treatment of Established Post-Operative Nausea and/or Vomiting

- Success: absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient.
 - Early: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Early: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of Post-Operative Nausea and/or Vomiting

- Success: absence of vomiting and/or retching in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively

- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of Nausea and/or Vomiting related to Chemotherapy

- Success: absence of vomiting and/or retching
 - during the first 24 hours of chemotherapy administration
 - acute/early vomiting and/or retching induced by highly emetogenic chemotherapy
 - acute/early vomiting and/or retching induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed/late vomiting and/or retching induced by highly emetogenic chemotherapy
 - delayed/late vomiting and/or retching induced by moderately emetogenic chemotherapy
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - during the first 24 hours of chemotherapy administration
 - acute: induced by highly emetogenic chemotherapy
 - acute: induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed: induced by highly emetogenic chemotherapy
 - delayed: induced by moderately emetogenic chemotherapy
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, worst day nausea/ vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention Radiation Induced Nausea and/or Vomiting

- Success: absence of vomiting and/or retching
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, worst day nausea/ vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of Nausea and/or Vomiting Associated with Pregnancy (including Hyperemesis Gravidarum)

- Success: absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman.
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
- Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes per period of time, number of or need for rescue medication, serious emetic sequelae, number of emesis-free days, re-hospitalization episodes and/or duration.

Wherever possible, data on effective dose range, dose-response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (headache, constipation, dizziness, sedation, etc.)

Study designs

1. For effectiveness, controlled clinical trials and good-quality systematic reviews.
2. For safety, in addition to controlled clinical trials, observational studies will be included.

The benefit of the RCT design is the ability to obtain a reliably unbiased estimate of treatment effects in a controlled setting. This is accomplished by using randomization to produce groups that are comparable based on both known and unknown prognostic factors.^{15, 16} However, RCTs can vary in quality, and often suffer from limitations in generalizability to the larger patient population. Observational study designs are thought to have greater risk of introducing bias, although they typically represent effects in a broader section of the overall patient population. While it has been shown that some observational studies and RCTs of the same treatments have similar findings, there are also multiple example of situations where this has not been true and the question of what type of evidence is best has not been resolved.^{17, 18} While RCTs also provide good evidence on short-term adverse events, observational designs are useful in identifying rare, serious adverse events which often require large numbers of patients exposed to a treatment over longer periods of time to be identified.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (February 2005 to October 2006). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 68 potentially relevant citations. Of those, there are 19 new potentially relevant controlled clinical trials (Appendix A).

New Drugs

None

New Indications

In June 2006, FDA granted approval for aprepitant use for prevention of nausea and vomiting associated with *moderately* emetogenic chemotherapy. Previously, aprepitant was only approved for prevention of nausea and vomiting associated with *severely* emetogenic chemotherapy.

New Safety Alerts

On June 23, 2006, Health Canada posted a notice regarding new contraindications for use of IV and oral forms of dolasetron (Appendix B). Contraindications include any use in children and adolescents and use in adults for prevention of post-operative nausea and vomiting. This warning comes after reports of “Cases of sustained supraventricular and ventricular arrhythmias, myocardial infarction and one case of fatal cardiac arrest.”

APPENDIX A

Cohen, I. T., D. Joffe, et al. "Ondansetron oral disintegrating tablets: acceptability and efficacy in children undergoing adenotonsillectomy." Anesthesia & Analgesia **101**(1): 59-63.

Postoperative nausea and vomiting (PONV), a major complication in children, is responsive to IV and oral ondansetron. Because these routes are not always available, we studied the acceptability and efficacy of ondansetron oral disintegrating tablets (ODT). In this double-blind, randomized, placebo-controlled study, 62 patients undergoing adenotonsillectomy, aged 5 to 11 years, preoperatively received ODT (4 mg) or placebo. Patients assessed the medication for taste and sensation. Anesthesia was induced with sevoflurane, maintained with desflurane, and supplemented with fentanyl 2.5 microg/kg and dexamethasone 0.5 mg/kg (maximum dose, 12 mg). An observer blinded to treatment evaluated patients for pain, agitation, and PONV. Postoperative treatment consisted of fentanyl 1 microg/kg for pain and agitation and metoclopramide 0.15 mg/kg (maximum dose, 10 mg) for PONV. There were no significant differences between study groups with regard to age, weight, recovery time, agitation, or pain. Approximately 90% of the subjects found the ODT to taste good. No subject rejected the study medication, but the ondansetron-containing tablets were found to be less palatable than the placebo. The incidence of vomiting was significantly less in the ondansetron-medicated group.

Corapcioglu, F. and N. Sarper (2005). "A prospective randomized trial of the antiemetic efficacy and cost-effectiveness of intravenous and orally disintegrating tablet of ondansetron in children with cancer." Pediatric Hematology & Oncology **22**(2): 103-14.

Orally disintegrating tablet (ODT) of ondansetron is a new formulation, which instantaneously disintegrates and disperses in the saliva without need for ingestion of a liquid. This makes the formulation suitable for administration in children. The objective of this study was to compare the relative efficacy and cost of ODT and intravenous (IV) formulation of ondansetron in controlling nausea and vomiting in children receiving chemotherapy regimens without cisplatin. This prospective randomized trial was performed in a single institution to compare ODT and IV formulation of ondansetron for the prevention of acute emesis in a group of 22 children. Study agents were administered 30 min before chemotherapy and 12 hourly after chemotherapy (5 mg/m² IV or 4-8 mg oral according to body surface area in 56 and 39 courses, respectively). After randomization, IV formulation was administered to some children instead of ODT due to unavailability of this formulation. Complete and major control of emesis was obtained in 92% of patients in the IV group and 93% of patients in the ODT group. In 56 courses with grade III-IV emetogenicity, complete response rates were not different between the two treatment arms. In the courses without corticosteroids complete response rates were not also different between the two arms. The mean costs per successfully controlled courses were 121.3 USD for the IV formulation whereas 63.2 USD for the ODT formulation. The results of this study confirmed that ODT formulation of ondansetron is a safe, well-tolerated, and cost-effective antiemetic for children during non-cisplatin-containing moderately and highly emetogenic chemotherapy.

D'Angelo, R., B. Philip, et al. (2005). "A randomized, double-blind, close-ranging, pilot study of intravenous granisetron in the prevention of postoperative nausea and vomiting in patients abdominal hysterectomy." European Journal of Anaesthesiology **22**(10): 774-9.

BACKGROUND AND OBJECTIVE: Postoperative nausea and vomiting (PONV) is a frequent and unpleasant experience that may increase postoperative complications and costs. For surgical procedures with a high risk of PONV, prevention is preferable to treatment. In this study, the authors explore the dose-response relationship between granisetron administered just prior to the end of surgery and post-operative nausea and vomiting in patients undergoing abdominal hysterectomy. **METHODS:** This was a randomized, double-blind, placebo-controlled, pilot study of post-operative nausea and vomiting prevention. Patients undergoing elective open abdominal hysterectomy requiring general anaesthesia received a single dose of granisetron 0.1, 0.2 or 0.3 mg or placebo administered approximately 15 min prior to the end of surgery. The primary efficacy end-point was the proportion of patients with no vomiting in the 0--6 h interval following medication administration. No inferential statistics were planned. **RESULTS:** The proportion of patients with no vomiting episode in the 0--6 h interval after administration of study medication was higher in each granisetron treatment group (>90%) than in the placebo group (77%). Proportions of patients with no vomiting episodes in the 0--24 h interval were similar across treatment groups. Results of analyses of proportions of patients with no moderate or severe nausea episodes, proportions of those requiring rescue medication and times to first use of rescue medication suggested a treatment effect of granisetron relative to placebo in both the 0--6 and 0--24 h intervals. Similar proportions of patients in each treatment group reported at least one adverse event. **CONCLUSIONS:** Granisetron at doses of 0.1, 0.2 and 0.3 mg administered just prior to the end of surgery suggested a trend of improved efficacy compared to placebo in preventing postoperative nausea and vomiting in the first 6 h after abdominal hysterectomy. This pilot study did not identify a dose-response relationship.

Freedman, S. B., M. Adler, et al. (2006). "Oral ondansetron for gastroenteritis in a pediatric emergency department." New England Journal of Medicine **354**(16): 1698-705.

BACKGROUND: Vomiting limits the success of oral rehydration in children with gastroenteritis. We conducted a double-blind trial to determine whether a single oral dose of ondansetron, an antiemetic, would improve outcomes in children with gastroenteritis. **METHODS:** We enrolled 215 children 6 months through 10 years of age who were treated in a pediatric emergency department for gastroenteritis and dehydration. After being randomly assigned to treatment with orally disintegrating ondansetron tablets or placebo, the children received oral-rehydration therapy according to a standardized protocol. The primary outcome was the proportion who vomited while receiving oral rehydration. The secondary outcomes were the number of episodes of vomiting and the proportions who were treated with intravenous rehydration or hospitalized. **RESULTS:** As compared with children who received placebo, children who received ondansetron were less likely to vomit (14 percent vs. 35 percent; relative risk, 0.40; 95 percent confidence interval, 0.26 to 0.61), vomited less often (mean number of episodes per child, 0.18 vs. 0.65; $P<0.001$), had greater oral intake (239 ml vs. 196 ml, $P=0.001$), and were less likely to be treated by intravenous rehydration (14 percent vs. 31 percent; relative risk, 0.46; 95 percent confidence interval, 0.26 to 0.79). Although the mean length of stay in the emergency department was reduced by 12 percent in the ondansetron group, as compared with the placebo group ($P=0.02$), the rates of hospitalization (4 percent and 5 percent, respectively; $P=1.00$) and of return visits to the emergency department (19 percent and 22 percent, $P=0.73$) did not differ significantly between groups.

CONCLUSIONS: In children with gastroenteritis and dehydration, a single dose of oral ondansetron reduces vomiting and facilitates oral rehydration and may thus be well suited for use in the emergency department. Copyright 2006 Massachusetts Medical Society.

Gan, T. J., A. Coop, et al. (2005). "A randomized, double-blind study of granisetron plus dexamethasone versus ondansetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing abdominal hysterectomy." *Anesthesia & Analgesia* **101**(5): 1323-9.

In this randomized, double-blind study, we evaluated whether small-dose granisetron (0.1 mg) plus dexamethasone 8 mg (G+D) was as effective as ondansetron 4 mg plus dexamethasone 8 mg (O+D) for preventing vomiting during the 0 to 2 h after tracheal extubation in patients undergoing abdominal hysterectomy requiring general anesthesia. Dexamethasone (D) was administered at induction of anesthesia, and granisetron (G) or ondansetron (O) was given approximately 15 min before tracheal extubation. Data on postoperative nausea and vomiting were collected at 0, 2, 6, and 24 h. For the primary efficacy endpoint, most patients in each group had no vomiting in the 0- to 2-h interval (82/87 [94%] for G+D versus 86/89 [97%] for O+D). Effectiveness of G+D was demonstrated versus O+D. Treatment groups were similar with regard to moderate or severe nausea, complete response, rescue medication use, and total control over 24 h. A descriptive assessment of adverse events showed that both combinations were well tolerated with infrequent and similar incidences of adverse events. The combination of small-dose G administered just before tracheal extubation plus D given at induction of anesthesia is an effective alternative to O+D in preventing vomiting during the 0- to 2-h interval after tracheal extubation.

Gralla, R. J., R. de Wit, et al. (2005). "Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two Phase III randomized clinical trials." *Cancer* **104**(4): 864-8.

BACKGROUND: The tendency of chemotherapeutic regimens to cause vomiting is dependent on the individual drugs in the regimen. The authors analyzed data combined from 2 Phase III trials to assess the effect of the neurokinin-1 (NK(1)) antagonist aprepitant combined with a 5HT(3) antagonist plus a corticosteroid in a subpopulation receiving > 1 emetogenic chemotherapeutic agent. **METHODS:** In the current study, 1043 cisplatin-naïve patients (42% were women) receiving cisplatin-based (> or = 70 mg/m²) chemotherapy were assigned randomly to a control regimen (ondansetron [O] 32 mg intravenously and dexamethasone [D] 20 mg orally on Day 1; D 8 mg twice daily on Days 2-4) or an aprepitant (A) regimen (A 125 mg orally plus O 32 mg and D 12 mg on Day 1; A 80 mg and D 8 mg once daily on Days 2-3; and D 8 mg on Day 4). Randomization was stratified for use of concomitant chemotherapy and female gender. The primary end point was complete response (no vomiting and no rescue therapy) on Days 1-5 (0-120 hours). Data were analyzed by a modified intent-to-treat approach, and logistic regression was used to make treatment comparisons among patients receiving the most frequently coadministered emetogenic concomitant chemotherapy (Hesketh level > or = 3). **RESULTS:** Among the approximately 13% of patients (n = 81 for A; n = 80 for control) who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33 percentage-point improvement

in the complete response rate compared with the control regimen. Among the general population, the advantage with aprepitant was 20 percentage points. CONCLUSIONS: The current analysis of > 1000 patients from 2 large randomized trials showed that in the subpopulation at increased risk of chemotherapy-induced nausea and vomiting due to concomitant emetogenic chemotherapy, the addition of aprepitant to standard antiemetics improved protection to an even greater extent than in the general study population.

Hartsell, T., D. Long, et al. (2005). "The efficacy of postoperative ondansetron (Zofran) orally disintegrating tablets for preventing nausea and vomiting after acoustic neuroma surgery." Anesthesia & Analgesia **101**(5): 1492-6.

Postoperative nausea and vomiting is a frequent complication of craniotomy. We evaluated the ability of intraoperative IV ondansetron followed by postoperative ondansetron in an orally disintegrating tablet formulation to reduce the frequency and severity of postoperative nausea and vomiting in a prospective, randomized, placebo-controlled double-blind trial of 60 patients undergoing acoustic neuroma resection. Each patient received intraoperative ondansetron (4 mg IV) or placebo 30 min before case end. Postoperatively, patients received ondansetron in an orally disintegrating tablet formulation (8 mg BID) or placebo twice a day for up to 72 h. Metoclopramide was available as rescue therapy for both groups. Severity of nausea (as measured on a 10-cm visual scale), number of emetic episodes, and requirement for rescue therapy were recorded. In the immediate postoperative period, nausea severity was less in patients treated with ondansetron than placebo (3.3 +/- 4.1 versus 7.3 +/- 4.2; $P < 0.001$) and fewer patients experienced vomiting (3 of 28 versus 11 of 32; $\chi^2 P < 0.01$). More patients required some form of rescue treatment in the placebo group on the first postoperative day (26 of 32 versus 16 of 28; $\chi^2 P < 0.01$). We conclude that after acoustic neuroma surgery IV ondansetron treatment prevents immediate postoperative nausea and vomiting. Postoperative treatment with ondansetron in an orally disintegrating tablet formulation was associated with less frequent rescue therapy as compared with placebo on the first postoperative day.

Herrstedt, J., H. B. Muss, et al. (2005). "Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy." Cancer **104**(7): 1548-55.

BACKGROUND: An aprepitant (APR) regimen was evaluated for prevention of nausea and emesis due to moderately emetogenic chemotherapy (MEC) over multiple cycles. METHODS: The authors performed a randomized, double-blind study. Eligible patients with breast carcinoma were naive to emetogenic chemotherapy and treated with cyclophosphamide alone or with doxorubicin or epirubicin. Patients were randomized to receive either an APR regimen (Day 1: APR 125 mg, ondansetron [OND] 8 mg, and dexamethasone [DEX] 12 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2-3: APR 80 mg every day) or a control regimen (Day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2-3: OND 8 mg twice per day). Data on nausea, emesis, and use of rescue medication were collected. The primary end point was the proportion of patients with a complete response (CR; no emesis or use of rescue therapy) in Cycle 1. Efficacy end points for the multiple-cycle extension were the probabilities of a CR in Cycles 2-4 and a sustained CR rate across multiple cycles. RESULTS: Of 866 patients randomized, 744 (85.9%) entered the multiple-cycle

extension, and 650 (75.1%) completed all 4 cycles. Overall, the CR was greater with the APR regimen over the 4 cycles: 53.8% versus 39.4% for Cycle 2, 54.1% versus 39.3% for Cycle 3, and 55.0% versus 38.4% for Cycle 4. The cumulative percentage of patients with a sustained CR over all 4 cycles was greater with the APR regimen ($P = 0.017$). CONCLUSIONS: The APR regimen was more effective than a control regimen for the prevention of nausea and emesis induced by MEC over multiple chemotherapy cycles.

Janicki, P. K., H. G. Schuler, et al. (2006). "Prevention of postoperative nausea and vomiting with granisetron and dolasetron in relation to CYP2D6 genotype." Anesthesia & Analgesia **102**(4): 1127-33.

We investigated the efficacy of granisetron and dolasetron in preventing postoperative nausea and vomiting. Because the metabolism of the various antiemetic 5-hydroxytryptamine type 3 (5-HT₃) antagonists involves different isoforms of the hepatic cytochrome P450 system, we examined the relationship between the clinical efficacy of these drugs and polymorphic cytochrome P450 2D6 (CYP2D6) genotype. This prospective, randomized, double-blind study involved 150 adult patients with a moderate to high risk for postoperative nausea and vomiting. All subjects received dexamethasone at induction of anesthesia followed by either 12.5 mg of dolasetron or 1 mg of granisetron. We analyzed the number of complete responders (no vomiting or rescue medication) during the first 24 hours after surgery. CYP2D6 genotyping was performed using a TaqMan real-time polymerase chain reaction. A complete response was more frequent in the granisetron group (54.7%) compared with the dolasetron group (38.7%, $P < 0.05$). In subjects receiving dolasetron, carriers of the duplication of the CYP2D6 allele predicting ultrarapid metabolizer status had more frequent vomiting episodes ($P < 0.05$) than patients in the granisetron group. It is postulated that the difference in the antiemetic efficacy between two investigated 5-HT₃ receptor antagonists may be associated with differences in the carrier status for the duplication of the CYP2D6 allele.

Jellish, W. S., J. P. Leonetti, et al. (2006). "Morphine/ondansetron PCA for postoperative pain, nausea, and vomiting after skull base surgery." Otolaryngology - Head & Neck Surgery **135**(2): 175-81.

OBJECTIVE: Patients who underwent skull base procedures have been noted to experience appreciable pain. This study examines pain after surgery and the effectiveness of patient controlled analgesia (PCA) with combination morphine ondansetron for analgesia and control of emesis. STUDY DESIGN AND SETTING: A total of 120 skull base surgery patients were randomized to receive placebo, morphine, or morphine ondansetron. Demographic and intraoperative variables were recorded along with pain, nausea, vomiting, and rescue analgesics. Total PCA use, hospital stay, satisfaction, and cost were also compared. RESULTS: Demographically the groups were similar. Pain was elevated with placebo PCA, and this group averaged twice as many analgesic rescues. Total usage time was lower with placebo PCA. Morphine ondansetron PCA had the lowest pain score with highest satisfaction. Nausea and vomiting was similar but female patients had more vomiting regardless of PCA group. CONCLUSIONS AND SIGNIFICANCE: The use of morphine PCA reduced pain and did not appreciably increase nausea or vomiting. The addition of ondansetron produced no real benefit and its PCA use cannot be justified. EBM rating: A-1b.

Khalil, S. N., A. G. Roth, et al. "A double-blind comparison of intravenous ondansetron and placebo for preventing postoperative emesis in 1- to 24-month-old pediatric patients after surgery under general anesthesia." *Anesthesia & Analgesia* **101**(2): 356-61.

We assessed the efficacy and safety of ondansetron (0.1 mg/kg IV) prophylactically administered before surgery for prevention of postoperative vomiting (POV) in a double-blind, placebo-controlled study of 670 pediatric patients, 1- to 24-mo-old, undergoing elective surgery under general anesthesia. The study enrolled 335 children in each treatment group (ondansetron versus placebo). Significantly fewer children treated with ondansetron exhibited emesis or discontinued the study prematurely after surgery (ondansetron, 11%; placebo, 28%; odds ratio = 0.33; $P < 0.0001$). The number required to treat prophylactically with ondansetron to prevent POV was approximately six. Ondansetron treatment also resulted in fewer patients requiring rescue medication or assumed to have had rescue upon early discontinuation from the study during the postoperative period (ondansetron, 5%; placebo, 10%) and less emesis (0 of 6) after rescue medication when compared with placebo (7 of 21). The incidence of POV and other antiemetic effects of ondansetron were similar in children aged 1-12 mo and 13-24 mo and in children prospectively expected or not expected to require opioids as part of their anesthetic or analgesic management. Ondansetron was well tolerated; the incidence of adverse events considered possibly related to study drug was similar between treatment groups (ondansetron, 1.8%; placebo, 1.5%). IMPLICATIONS: This prospective, randomized, double-blind, placebo-controlled study establishes the efficacy and tolerability of IV ondansetron (0.1 mg/kg) in the prevention of postoperative emesis in 1- to 24-mo-old pediatric patients undergoing elective surgery under general anesthesia.

Kocamanoglu, I. S., S. Baris, et al. (2005). "Effects of granisetron with droperidol or dexamethasone on prevention of postoperative nausea and vomiting after general anesthesia for cesarean section." *Methods & Findings in Experimental & Clinical Pharmacology* **27**(7): 489-93.

This prospective, placebo-controlled, double-blinded, and randomized study was undertaken to compare the efficacy of granisetron, droperidol, and combinations of granisetron with droperidol or dexamethasone on postoperative nausea and vomiting in patients undergoing general anesthesia for cesarean section. Patients ($n = 150$) who were scheduled for cesarean section under general anesthesia were randomly assigned to one of the five groups: physiological saline 5 ml in Group A, granisetron 40 microg/kg + dexamethasone 8 mg in Group B, granisetron 40 microg/kg + droperidol 1.25 mg in Group C, droperidol 1.25 mg in Group D, and granisetron 40 microg/kg in Group E were administered intravenously after clamping of the fetal umbilical cord. Postoperative nausea and vomiting was observed for 0-24 h after the anesthesia. Cesarean sections were all performed under general anesthesia. Postoperative nausea and vomiting was more common in placebo group (56.7%) than the others during the 0-24 h after the anesthesia ($p < 0.05$). All granisetron groups were more effective than placebo and droperidol groups during the postoperative 3-24 h ($p < 0.01$). Although this trial lacks statistical power, granisetron alone and combinations with droperidol or dexamethasone were effective similarly. All treatment groups, except droperidol during the postoperative 3-24 h, were effective for prevention of postoperative nausea and vomiting during the postoperative 0-24 h. (c) 2005 Prous Science. All rights reserved.

Meyer, T. A., C. R. Roberson, et al. (2005). "Dolasetron versus ondansetron for the treatment of postoperative nausea and vomiting.[erratum appears in Anesth Analg. 2005 Jul;101(1):43]." Anesthesia & Analgesia **100**(2): 373-7.

The management of postoperative nausea and vomiting (PONV) remains a persistent problem. Despite the use of prophylactic antiemetics, breakthrough nausea and vomiting still frequently occur. There have been no published studies comparing dolasetron and ondansetron for the treatment of PONV. This was a prospective, randomized, double-blind, active-controlled study in adult outpatient surgery patients. We screened 559 consecutive adult surgery patients, with 92 patients randomized to either ondansetron or dolasetron. The objectives of the study were 1) to determine whether treatment of PONV with ondansetron 4 mg IV or dolasetron 12.5 mg IV would result in better outcomes in patients undergoing day surgery and 2) to compare the cost of drugs used for treating PONV. Thirty-three (70%) of 47 patients given ondansetron required rescue medication, compared with 18 (40%) of 45 patients given dolasetron ($P < 0.004$). Dolasetron was approximately 40% less expensive than ondansetron, and the costs of the study drug plus rescue antiemetics were 30% less in the dolasetron group than in the ondansetron group. Dolasetron provided greater efficacy for antiemetic treatment because of the need for less rescue therapy. Because of the decreased use of rescue antiemetics and acquisition cost at our hospital, costs in the dolasetron group were less than costs in the ondansetron group.

Pirat, A., S. F. Tuncay, et al. (2005). "Ondansetron, orally disintegrating tablets versus intravenous injection for prevention of intrathecal morphine-induced nausea, vomiting, and pruritus in young males." Anesthesia & Analgesia **101**(5): 1330-6.

In this study we compared the efficacy of orally disintegrating tablets (ODT) and IV ondansetron for preventing spinal morphine-induced pruritus and postoperative nausea and vomiting (PONV) in healthy young male patients. Patients who received bupivacaine with 0.20 mg morphine for spinal anesthesia were randomly assigned to the ODT group (ODT ondansetron 8 mg, $n = 50$), the IV group (4 mg ondansetron IV, $n = 50$), or the placebo group ($n = 50$). Each individual was assessed for pruritus, postoperative nausea and vomiting, and pain at 0, 2, 6, 12, 18, and 24 h after surgery using three distinct visual analog scales. The frequencies of postoperative nausea and vomiting and frequencies of requirement for rescue antiemetic and antipruritic were recorded. There were no significant differences among the three groups with respect to incidence or severity of PONV or postoperative pain visual analog scale scores. The incidences of pruritus in the ODT (56%) and IV (66%) groups were significantly different from that in the placebo group (86%) ($P < 0.02$ for both). Only the ODT group had significantly lower mean pruritus visual analog scale scores at 0, 2, 6, and 12 h postsurgery than the placebo group ($P < 0.023$ for all). The frequency of requirement for rescue antipruritic was significantly less in the ODT group than the placebo group ($P = 0.013$). Both ODT ondansetron 8 mg and IV ondansetron 4 mg are more effective than placebo for preventing spinal morphine-induced pruritus, but neither form of this agent reduces spinal morphine-induced postoperative nausea and vomiting in this patient group.

Purhonen, S., E. M. J. Koski, et al. (2006). "Efficacy and costs of 3 anesthetic regimens in the prevention of postoperative nausea and vomiting." Journal of Clinical Anesthesia **18**(1): 41-5.

STUDY OBJECTIVE: The aim of the study was to compare the antiemetic efficacy and costs associated with 3 different anesthesia regimens used in gynecologic laparoscopy.

DESIGN: This was a randomized, controlled study. **SETTING:** The study was conducted at a university hospital. **PATIENTS:** We studied 150 ASA physical status I or II patients, undergoing elective gynecologic laparoscopy with general anesthesia. **INTERVENTION:** Patients were allocated into the following 3 groups: group P-preoperative placebo tablet, propofol induction, propofol-air/O₂ maintenance; group I + O-preoperative 8-mg ondansetron tablet, thiopental induction, isoflurane-N₂O maintenance; group I (control)-preoperative placebo tablet, thiopental induction, isoflurane-N₂O maintenance. **MEASUREMENTS:** The frequency of postoperative nausea and vomiting (PONV), number needed to treat to prevent PONV, and the costs of the anesthetic drugs to prevent PONV in one additional patient were evaluated. **MAIN RESULTS:** The frequency of PONV within the 24-hour study period was lowest in group I + O (P, 38%; I + O, 33%; and I, 59%; $P < 0.05$ I + O vs I). The number needed to treat was 5 in group P and 4 in group I + O, compared with group I. The median costs of anesthetic drugs to prevent PONV in one additional patient were \$65 in group P and dollar 68 in group I + O, compared with group I. **CONCLUSIONS:** We conclude that in gynecologic laparoscopy, propofol-air/O₂ anesthesia alone, and isoflurane-N₂O anesthesia combined with an oral 8-mg dose of ondansetron had similar efficacy and costs to prevent PONV. Isoflurane-N₂O anesthesia without ondansetron was less expensive, but was also less efficacious.

Purhonen, S., M. Niskanen, et al. (2006). "Supplemental 80% oxygen does not attenuate post-operative nausea and vomiting after breast surgery." *Acta Anaesthesiologica Scandinavica* **50**(1): 26-31.

BACKGROUND: Although supplemental oxygen has been shown to be as effective as ondansetron in the prevention of post-operative nausea and vomiting (PONV) in one study in abdominal surgery patients, the antiemetic efficacy of supplemental oxygen is controversial on the basis of studies with other patients. We compared the efficacy of 80% and 30% oxygen in decreasing PONV in breast surgery. Ondansetron was used as an active control. **METHODS:** Ninety patients were given a standardized sevoflurane anesthetic. They were randomly assigned to three groups: 30% oxygen in nitrogen and saline 2 ml intravenously (i.v.) at the end of surgery (group 30); 80% oxygen in nitrogen and saline 2 ml (group 80); and 30% oxygen in nitrogen and ondansetron 4 mg (group O). Oxygen was administered during surgery and up to 2 h after surgery. **RESULTS:** The incidence of total response (no retching or vomiting, no nausea) during the first 24 post-operative hours was not different between group 80 (17%) and group 30 (11%) but was higher in group O (43%) than in group 30 ($P < 0.05$). Compared with group O, patients in group 80 experienced more vomiting during the study period 0-24 h (66% vs. 32%; $P < 0.05$) and more nausea during the period 6-24 h (72% vs. 39%; $P < 0.05$). There was no difference between the groups in their risk for PONV, pain scores, opioid consumption, or patient satisfaction. **CONCLUSIONS:** In this study, supplemental 80% oxygen administration failed to decrease PONV in breast surgery.

Sarvela, P. J., P. M. Halonen, et al. (2006). "Ondansetron and tropisetron do not prevent intraspinal morphine- and fentanyl-induced pruritus in elective cesarean delivery." *Acta Anaesthesiologica Scandinavica* **50**(2): 239-44.

BACKGROUND: Although intraspinal morphine has been shown to be effective in providing analgesia after cesarean delivery, pruritus as a side-effect remains a common cause of dissatisfaction. The role of ondansetron has been studied in preventing pruritus

but the results have been contradictory. **METHODS:** We randomized 98 parturients undergoing elective cesarean section using combined spinal-epidural anesthesia into a double-blinded trial to receive tropisetron 5 mg (T group) or ondansetron 8 mg (O group) or placebo (NaCl group) after delivery, when intrathecal morphine 160 microg and fentanyl 15 microg were used for post-operative pain control. The patients additionally received ketoprofen 300 mg per day. Post-operative itching, nausea and vomiting, sedation and need for rescue analgesics were registered every 3 h up to 24 h, and all patients were interviewed on the first post-operative day. **RESULTS:** Seventy-six percent of the parturients in the placebo group, 87% in the ondansetron, and 79% in the tropisetron group had itching. The incidence of post-operative nausea and vomiting was 21%, 20% and 11% of the patients in the placebo, ondansetron and tropisetron groups, respectively. Medication for pruritus was needed by 31%, 23% and 39% of the patients in the placebo, ondansetron and tropisetron groups, respectively. In the post-operative questionnaire, the patients reported less post-operative nausea in the tropisetron group than in the placebo group ($P < 0.01$). **CONCLUSION:** Neither ondansetron nor tropisetron prevent itching caused by intrathecal morphine with fentanyl. However, tropisetron reduced post-operative nausea.

Treschan, T. A., C. Zimmer, et al. (2005). "Inspired oxygen fraction of 0.8 does not attenuate postoperative nausea and vomiting after strabismus surgery." *Anesthesiology* **103**(1): 6-10.

BACKGROUND: Postoperative nausea and vomiting (PONV) is a distressing problem after strabismus surgery. An inspired oxygen fraction has been reported to decrease PONV in patients after colon resection and to be more effective than ondansetron after gynecologic laparoscopy. Therefore, in a randomized, prospective, placebo-controlled study, the authors tested whether an inspired oxygen fraction of 0.8 decreases PONV in patients undergoing strabismus surgery and whether oxygen is more effective than ondansetron. **METHODS:** With approval of the authors' institutional review board, 210 patients were randomly assigned to receive one of three treatments: (1) 30% inspired oxygen in air plus intravenous administration of saline, (2) 80% inspired oxygen in air plus intravenous administration of saline, or (3) 30% inspired oxygen in air plus 75 microg/kg ondansetron intravenously during induction. General anesthesia was standardized and included etomidate, alfentanil, and mivacurium for induction and sevoflurane for maintenance. PONV was evaluated 6 and 24 h postoperatively by an investigator unaware of treatment assignment. **RESULTS:** Overall postoperative incidence of nausea and vomiting was 41% for inspired oxygen fraction of 0.3 plus placebo, 38% for inspired oxygen fraction of 0.8 plus placebo, and 28% for inspired oxygen fraction of 0.3 plus ondansetron, respectively ($P = 0.279$). Therefore, there was no statistically significant difference of PONV incidence among groups.

CONCLUSIONS: An inspired oxygen fraction of 0.8 during general anesthesia with sevoflurane does not decrease PONV in patients undergoing strabismus repair. Ondansetron also did not significantly decrease PONV in our study setting.

White, P. F., J. Tang, et al. (2006). "The use of oral granisetron versus intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery." *Anesthesia & Analgesia* **102**(5): 1387-93.

Based on comparative studies in patients receiving emetogenic chemotherapy, it has been suggested that granisetron would be more effective than ondansetron for the prevention

of postdischarge nausea and vomiting (PDNV). However, there have been no direct comparisons of these two popular 5-HT₃ antagonists with respect to PDNV and quality of recovery. We designed this randomized, double-blind study to compare the antiemetic efficacy of oral granisetron (1 mg) to a standard IV dose of ondansetron (4 mg) when administered for antiemetic prophylaxis as part of a multimodal regimen in a laparoscopic surgical population. A total of 220 patients undergoing laparoscopic surgery with a standardized general anesthetic technique were enrolled in this prospective study at two major medical centers. Patients were randomly assigned to one of two prophylactic treatment groups: the control (ondansetron) group received an oral placebo 1 h before surgery and ondansetron, 4 mg IV, at the end of the surgery, and the granisetron group received granisetron, 1 mg per os, 1 h before surgery, and normal saline, 2 mL IV, at the end of the surgery. The early recovery profiles, requirement for rescue antiemetics, incidence of PDNV, and the side effects were recorded over the 48 h study period. In addition, nausea scores were assessed using an 11-point verbal rating scale at specific intervals in the postoperative period. The quality of recovery and patient satisfaction scores were recorded at 48 h after surgery. The demographic characteristics were similar in the two prophylaxis treatment groups, as well as the recovery times to patient orientation, oral intake, and hospital discharge. The incidences of PDNV, requirements for rescue antiemetics, and quality of recovery did not differ between the two study groups. The antiemetic drug acquisition costs to achieve comparable patient satisfaction with ondansetron and granisetron were US 25.65 dollars and 47.05 dollars, respectively. Therefore, ondansetron (4 mg IV) was more cost-effective than granisetron (1 mg per os) for routine antiemetic prophylaxis as part of a multimodal regimen in patients undergoing either outpatient or inpatient laparoscopic surgery.

APPENDIX B

June 23, 2006

To: Hospital Chief of Medical Staff; Canadian Paediatric Society;
Canadian Oncology Societies; Cancer Centres; Canadian
Anaesthesiologists Society.

Please forward to the relevant Departments (Medical Directors, Intensive Care Units; Directors of Nursing, Intensive Care Units; Director, Department of Pediatrics; Director, Department of Anaesthesiology; Director, Department of Pharmacy, Departments of Oncology, Radio-Oncology, Nuclear Medicine, etc) and involved professional staff and please **post** this NOTICE.

PR ANZEMET® is contraindicated for:

Any therapeutic use in children and adolescents under 18 years of age.

The prevention and treatment of post-operative nausea and vomiting in adults.

These contraindications apply to *both* intravenous (IV) and oral formulations.

Cases of sustained supraventricular and ventricular arrhythmias, myocardial infarction and one case of fatal cardiac arrest have been reported in association with ANZEMET® (dolasetron mesylate) use in both children and adolescents.

Since the results of pharmacokinetic studies of ANZEMET® indicate a decrease in drug clearance with increasing age, the risk/benefit ratio for the use of ANZEMET® in post-operative patients 18 years of age and older is also negative.

The Canadian ANZEMET® label has carried warnings about QTc prolongation and the description of serious cardiovascular adverse reactions since approval in 1997. Although ANZEMET® has never been indicated for use in children in Canada, Health Canada is aware of the off-label use of this product in the pediatric population. Health Canada is also aware of the off-label use of ANZEMET® in adults for the treatment of post-operative nausea and vomiting. ANZEMET® is **only** indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin, in adults.

Health Canada is requesting all manufacturers of the drugs in this class (5-HT₃ antagonists, ANZEMET®, KYTRIL®, and ZOFTRAN®) to conduct thorough analyses of their safety databases. Following review of these data, Health Canada will take action as appropriate.

At this time, Health Canada is reminding health care providers to strictly adhere to the dosing recommendations in the Product Monographs of these drugs.